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Acute Pancreatitis by liposomal amphotericin B. Case report and review of the literature

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ABSTRACT

BACKGROUND: *The most frequently observed adverse reactions of a liposomal formulation of amphotericin B (LAB) on the first dose of fever and rigors are, hypokalemia and renal toxicity. Acute pancreatitis is not listed in the Summary of Product Characteristics of LAB, although some non-severe cases of pancreatitis toxicity after LAB are described in the literature.*

CASE SUMMARY: *We present the case of an 88-year-old male with not known allergies and diagnosed with arterial hypertension and Grade III chronic kidney disease. One month before was admitted because of pneumonia, acute kidney injury, atrial fibrillation and pancytopenia; he was discharged on January 13, 2016, and two weeks later, he returned to the Urgency Department with severe deterioration of the general condition, fever, and a skin rash , these symptoms were attributed to a delayed allergic reaction to levofloxacin. During his first admission, he was treated with acetylsalicylic acid 100 mg, digoxin, metamizole, pantoprazole, valsartan/amlodipine.*

The Lab results showed pancytopenia .It was performed a bone marrow aspiration, suggesting a case of leishmaniasis. It was initiated intravenous treatment with LAB at 3 mg / kg / day. The first day of treatment, the patient showed a severe bronchospasm, exacerbation of the previous rash possibly caused by quinolones treatment, was treated with corticosteroids, antihistamines, aerosol therapy and oxygen therapy until full recovery.

During the following days, LAB was administrated at a slow infusion rate and premedication with appropriate tolerance. On the fifth day of the treatment, the patient started with a diffuse abdominal pain, anorexia, and vomiting. The amylase lab result was 431 IU/L. An abdominal scanner showed edematous pancreatitis. After 48 hours the amylase and lipase lab values were normal. And the abdominal Scanner was repeated with no changes. The evolution of patient was aggravating until reaching multiple organs failure a few days later the patient died.

CONCLUSION: We have described the first case report of pancreatitis LAB-induced resulting in death.

Keywords: case-report, *liposomal amphotericin B*, pancreatitis, Adverse-drug reaction, *leishmaniasis*.
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1. Introduction

The liposomal amphotericin B (LAB) is an antifungal polyene macrolide produced from Streptomyces nodosus. The liposomal formulation makes the drug go integrated inside spherical structures, which walls are joined to a phospholipid bilayer. These Liposomes allows the diffusion of the antifungal into the tissues where the LAB is liberated. LAB acts joining sterols of the membranes of the sensitive fungi forming pores that cause intracellular potassium output and alterations in the permeability which finishes destructuring the fungal cell. LAB is indicated in the treatment of systemic fungal infections by filamentous fungi (Aspergillus, Mucorales) and yeast, Cryptococci meningitis, endemic mycoses as well as in cases of visceral leishmaniasis. In addition, its use is accepted in the prophylactic and empirical treatment in hematologic patients with severe neutropenia. [(1)]

The most frequently observed adverse reactions of LAB from infusion reactions are hypokalemia and renal toxicity. Acute pancreatitis is a rarely described adverse event associated with LAB and it is not listed in the Summary of Product Characteristics of LAB.

This report gives a detailed description of acute pancreatitis by LAB resulting ultimately in the patient´s death.

2. Case report

An 88-year-old male was admitted to the Emergency Department of La Paz Hospital (Madrid) with severe deterioration of his general condition, fever and skin rash predominantly in the trunk and extremities which were attributed to a delayed allergic reaction to levofloxacin initiated 5 days before. Lab results showed pancytopenia with hemoglobin: 8,9 gr/dL, leukocytes 1500/mm3 and 50.000 platelets/UI, C-Reactive Protein : 8,5 mg/L. The patient history included arterial hypertension and Grade III chronic kidney disease secondary to chronic hydronephrosis, radical cystectomy with neobladder reconstruction due to bladder cancer extirpation eleven years ago. Not known allergies, no alcohol intake. The patient lived in the urban area during the week and on the weekends in the countryside. He did not have any pet, did not travel abroad and did not have any other epidemiological risk factors. The patient was independent on the basic activities of life. One month ago he was admitted to the hospital due to pneumonia, acute kidney injury, atrial fibrillation and pancytopenia; he was treated with levofloxacin, corticosteroids, and aerosol therapy during 14 days and discharged.

A bone marrow aspiration (BMA) was performed showing intracellular incorporations with macrophages, monocytes and some segmented neutrophils, compatible with presence intracellular parasites suggestive of leishmaniasis. With the diagnosis of visceral leishmaniasis a treatment with intravenous LAB at 3 mg / kg / day was initiated. On the first day of treatment, after one hour of infusion, the patient showed a severe bronchospasm and exacerbation of the previous rash; he was treated with corticosteroids, antihistamines, aerosol therapy and oxygen therapy with full recovery.

During the following days with LAB the patient showed appropriate tolerance after the use of premedication (corticosteroids, analgesics, and antihistamine drugs) and a slower infusion rate.

On the fifth day of LAB treatment, the patient presented a diffuse abdominal pain, anorexia, and vomiting. Lab results were as follows: amylase 431 IU/L (Normal Range 30-118 UI/L), ALT < 8 UI/L, alkaline phosphatase41 UL/L, total bilirubin 0,3 mg/dl, serum creatinine 1,20 mg/dl and calculated glomerular filtration rate was 53 ml/min/1,73m2 (CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration). The abdominal scanner showed no signs of tumor recurrence, no significant alterations in the liver, showed splenomegaly with parenchymal infarcts, and discreet trabeculae of fat in pancreatic cells, especially around the head. Edematous pancreatitis was diagnosed and basal Ranson Criteria of pancreatitis severity [(2)] was 1/5 with an estimated mortality < 1%. LAB was withdrawn and the other medications maintained (acetylsalicylic acid 100 mg, digoxin, metamizole, pantoprazole, valsartan/amlodipine). After 48 hours lab results of amylase and lipase were within the normal range; liver lab parameters remained normal. An abdominal scanner was repeated with no changes. Ranson criteria at 48 hours was 5/6 (BUN 49,93 mg/dl, Calcium < 7,3 mg/dl, Base excess – 5 mEq, fluid sequestration of 6 liters), with an estimated mortality of 10-20%. Ionic calcium corrected by Ph was 1.17 mg/dl (NR < 1.32 mg/dl), triglycerides 129 mg/dl (NR<150 mg/dl). Microbiological results were: negative for HIV, Cytomegalovirus: IgG positive and IgM negative; Toxoplasma:IgG positive, Ig M negative; EBV VCA-IgM negative, EBNA antibody (CLIA) positive.

From then, the patient remained to fast with high contribution of fluid therapy; evolution progressed negatively with disseminated intravascular coagulation and multiple organ failures and a few days later the patient died.

According to Spanish data protection law, we obtained the informed consent signed by patient's relatives.

3. Discussion

Up to 20% of adverse drug reactions (ADR) by LAB are related to the rapid perfusion of the drug with fever, bronchospasm, rash, nettle-rash and muscular widespread pain. These ADRs are usually solved with the administration of premedication and slowing the infusion rate. The most frequent (>10%) ADRs of LAB by organs are: Nervous system: insomnia (17% to 22%); Cardiovascular: Peripheral edema (15%); Skin and subcutaneous: pruritus (11%); Gastrointestinal and hepatobiliary: nausea (16% to 30%), vomiting (11% to 32%), diarrhea (11% to 30%), increased ALT (15%), increased AST (13%); Renal and urinary: increase of creatinine (18% to 40%); Blood and lymphatic system: anemia (27% to 48%); Respiratory, thoracic and mediastinal: Dyspnea (18% to 23%); Metabolism and nutrition: hypomagnesemia (15% to 50%), hypokalemia (31% to 51%). Other common reactions are hypertension (8% to 19%), tachycardia (9% to 19%), and headache (9% to 20%).

In the Summary of Product Characteristics of LAB, it is described that dose adjustments are not necessary for patients with impaired renal function or elderly patients. Also, it is not described acute pancreatitis within it.

Table 1 summarized the studies and cases-reports of acute pancreatitis by LAB [3,4,5,6].

The notifications to the FDA, from January of 2004 to October of 2012, of patients, taking LAB and developing pancreatitis were 31 cases, this represents a 1.15% of RAM related to this antifungal.[7] In any of the published reports or studies of LAB-associated to acute pancreatitis have reported relevant information about the renal function. It is described that when the amphotericin B was replaced with LAB a significant improvement in the clinical tolerability of the drug was observed, including fewer cases of acute kidney failure. However, LAB also gives rise to increases in serum creatinine. [8-10]

The mechanism of pancreatitis by LAB remains unclear. LAB was designed to enhance drug accumulation in phagolysosomes within the same phagocytes that harbor the fungi. As these phagocytes traffic to and accumulate in the spleen, the antifungal drug amphotericin B gains direct access to the intravesicular sites (i.e., phagolysosomes within macrophages and phagocytes) of fungal growth without having to resort to ligand–receptor interactions. Also, lipid-formulated drug reduces renal toxicity, reducing off-target (renal) drug accumulation and toxicity.[11] Non-lipid amphotericin B formulation exhibits renal toxicity because of drug aggregation and

Table 1:

REFERENCE	CASE SUMMARY	DRUGS	TYPE OF REPORT
A. Stuecklin-Utsch et al.[3]	Performed a retrospective analysis of 31 oncology pediatric patients who had received LAB at accumulative dose between 3,5 to 20 mg Kg. In five patients, an isolated transient elevation of serum lipase level during or shortly after the therapy with LAB was detected. Three of these patients showed clinical signs of pancreatitis, with one patient displaying slightly elevated transaminases.	Liposomal Amphotericn B	Retrospective cohort
R. López Almaraz et al [4]	Described one case of acute pancreatitis developed 12 hours after the anesthesia with propofol in an oncology adolescent patient treated with LAB, imipenem , ciprofloxacin and trimethoprim-Sulfamethoxazole.	Liposomal amphotericin B (Ambisome) Propofol Trimethoprim -Sulfamethoxazole	Case report Causality algorithm of Karch y Lasagna
F. Meunier et al.[5]	Described one case of pancreatitis in a patients with hepatosplenic candidiasis among 126 adults treated with LAB.	Liposomal amphotericin B (Ambisome)	Multicentre compassionate study
O. Ringdén at al.[6]	Evaluated the safety of LAB in 187 transplant recipients treated with cyclosporin and observed one single case of pancreatitis.	Liposomal amphotericin B (Ambisome) Ciyclosporin	Restrospective cohort

accumulation in renal tissues, but, to our knowledge it had not been reported in any case of pancreatitis, so that a possible mechanism for pancreatitis caused by amphotericin formulated in liposomes could be an enzyme induction due to fat overload or a toxic damage of the pancreatic tissue by the liposomes.

The causality assessment was performed using the algorithm of the Spanish Pharmacovigilance System.[12]This algorithm evaluates the following parameters: the chronology referred as the interval between drug administration and effect, the literature defining the degree of knowledge of the relationship between the drug and effect, the evaluation of drug withdrawal, the rechallenge effect, and the alternative causes. The final evaluation is listed as improbable (not related), conditional (not related), possible (related), probable (related) or definitive cases (related). Alternative causes of pancreatitis: gallstones, alcohol intake, infectious agents, cancer recurrence, hypercalcemia, hypertriglyceridemia were reasonably discarded. In our patient exits chronology (+2), withdrawal effect (+2) literature (+1), no alternatives causes (+1) In order to establish the diagnosis of pancreatitis we used led to an assessment of "probable" (+6) relationship.

In conclusion, LAB-induced pancreatitis represents a not well established ADR. This is the first case report of mortal pancreatitis due LAB therapy. It is important to know that although rarely but severe pancreatitis can occur in patients with LAB treatment and must be taken into account by clinicians. This case has been reported to the Pharmacovigilance Centre in Madrid (registered as number 13-605796). [13]

4. References

[1] *Summary of Product Characteristics* AMBISOME (SPC AMBISOME), last version: January 2016. [available from www.aemps.gob.es/cima]

[2] Swaroop Vege S ,Grover S. Predicting the severity of acute pancreatitis In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.[available from http://www.uptodate.com/]

[3] Stoecklin-Utsch A, Hasan C, Bode U, Fleischhack G. Pancreatic toxicity after liposomal amphotericin B. Mycoses. 2002 Jun;45(5-6):170-3. PubMed PMID: 12100534.

[4] López Almaraz R, García Sáiz MM, Montesdeoca Melián A, Requena Quesada GM. [Acute pancreatitis after anesthesia with propofol in a teenage boy treated with liposomal amphotericin B]. An Pediatr (Barc). 2004;60:480-1.

[5] Meurier F, Prentice HG, Ringden O. Liposomal amphotericin B (AmBisome®): safety data from a phase II/III clinical trials. J Antimicrob Chemother 1991; 28 (Suppl B): 83-91

[6] Ringden O, Andstroem E, Remberger M, Svahn BM, Tollemar J. Safety of liposomal amphotericin B (AmBisome_) in 187 transplant recipients treated with cyclosporin. Bone Marrow Transpl 1994; 14 (Suppl. 5), 10–14.

[7] About this FacMed analysis covering adverse side effect reports of Ambisome patients who develop pancreatitis in:FacMed. [Available from http://www.FacMed.com]

[8] Moreau P,Milpied N, FayetteN et al. Reduced renal toxicity and improved clinical tolerance of amphotericin mixed with Intralipid compared with conventional amphotericin B in neutropenic patients. J Antimicrob Chemother. 1992 Oct ; 30 (4) : 535-41

[9] Caillot D,Casasnovas O, SolaryE at al. Efficay and tolerance of an amphotericin B lipid (Intralipid) emulsion in the treatment of candidemia in neutropenic patients. J Antimicrob Chemother. 1993 Jan ; 31 (1): 161-9

[10] Kirsh R, Goldsteins R, Tarloff J et al An emulsion formulation of amphotericin B improves the therapeutics index when treating murine candidiasis. J Infect Dis. 1988 Nov ; 158 (5): 1065-70

[11] Kraft JC, Freeling JP, Wang Z, Ho RJ. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. JPharmSci. 2014;103:29-52.

[12] Capellá D, Laporte, JR. La notificación espontánea de reacciones adversas a medicamentos. In Principios de Epidemiología del Medicamento 2nd edn. (eds. Laporte JR &Tognoni G) 147–170 (Masson-Salvat, Barcelona, 1993).

[13] Electronic form to report suspected adverse reactions to medications. Spanish Pharmacovigilance System for Medicinal Products for Human Use [Available from http://www.notificaram.es]